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Delay of Brain Development and Maturation in Pups Undergoing to Maternal Hyperhomocysteinemia †

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Abstract: The effect of the toxic amino acid homocysteine on both: mother and embryo causes disruption of placental blood flow and can lead to disturbances of the brain formation in offspring. The molecular and cellular mechanisms of these effects are poorly studied. The effects of maternal hyperhomocysteinemia (mHHC) on the neuronal migration, neural tissue maturation and expression of some neuronal genes were analyzed. mHHC was induced in female rats by per os administration of 0.15% aqueous methionine solution from the 4th day of pregnancy until delivery. Ultrastructure of both cortical and hippocampus tissue in mHHC pups demonstrated the developmental delay, accompanied by a retardation in motor development and body weight. The absence of synaptic glomeruli in hippocampus tissue of P20 mHHC pups suggested more essential delay in development compared to the cortical tissue. Neuronal cells labeled on E14 or E18 showed decreased number and disturbed positioning, indicating mHHC disrupted both generation and radial migration of the neuroblasts into the cortical plate. In E14 mHHC fetus brain there were decreased expression of the Kdr gene (an angiogenesis system component) and increased content of SEMA3E and the MMP-2 activity level. On E20 the level of Bdnf gene expression was increased in mHHC group. The increase in proBDNF/mBDNF ratio might affect neuronal cell viability, positioning and maturation in mHHC pups. The decrease in the level of procaspase-8 with Caspase-3 activation in the brain of E20 mHHC fetuses may indicate the development of apoptosis. It can be concluded that mHHC disturbs the mechanisms of early brain development leading to the delay in brain tissue maturation in neocortex and hippocampus of pups during the first month of their postnatal ontogenesis.

Keywords: hyperhomocysteinemia, rat, hippocampus, brain cortex

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